

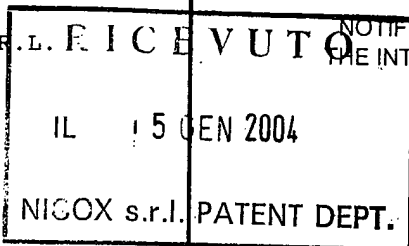
PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

NICOX RESEARCH INSTITUTE S.R.L. RICEVUTO
Patent Department
Attn. BARCHIELLI, Giovanna
Via L. Ariosto 21
I-20091 Bresso (MI)
ITALY



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference HF 2557/061/PCT	Date of mailing (day/month/year) 13/01/2004
International application No. PCT/EP 03/00394	International filing date (day/month/year) 16/01/2003
Applicant NICOX S.A.	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Marthe Oldendorf
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J41/00 C07J43/00 A61K31/573 A61K31/58 A61P5/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TALLET ET AL: "NO-Steroids: Potent Anti-inflammatory Drugs with Bronchodilating Activity in Vitro" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 290, no. 1, 11 January 2002 (2002-01-11), pages 125-130, XP002210203 ISSN: 0006-291X	1,4,5, 8-26
Y	page 126, column 1, paragraph 3 page 126, column 1, last paragraph page 126, column 2; figure 1 page 127, column 1, last paragraph page 128, column 1, last paragraph page 129, column 1, paragraphs 1,4,5 page 129, column 2, paragraph 2 --- -/--	2,3

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 December 2003

Date of mailing of the international search report

13. 01. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D2 X	PAUL-CLARK M ET AL: "21-NO-PREDNISOLONE IS A NOVEL NITRIC OXIDE-RELEASING DERIVATIVE OF PREDNISOLONE WITH ENHANCED ANTI-INFLAMMATORY PROPERTIES" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 131, December 2000 (2000-12), pages 1345-1354, XP001088964 ISSN: 0007-1188	1,4,5, 8-26
Y	page 1346, column 2; figure 1 page 1348, column 2, paragraph 2 page 1349, column 1, paragraph 1 page 1349, column 2, paragraph 1 page 1350, column 1, paragraph 2 page 1350, column 2, paragraph 1 page 1351, column 2, paragraph 2 page 1353, column 2, paragraph 1	2,3
D3 X	KEELBE J ET AL: "VASORELAXANT EFFECT OF NITRIC OXIDE RELEASING STEROIDAL AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 133, no. 7, August 2001 (2001-08), pages 1023-1028, XP001088994 ISSN: 0007-1188	1,4,5, 8-26
Y	page 1024, column 2, paragraph 3 page 1025, column 1; figure 1 page 1026, column 2, paragraph 3 page 1027, column 2, last paragraph	2,3
D4 Y	JENSEN, EJVIND ET AL: "N-Substituted (aminomethyl)benzoate 21-esters of corticosteroids as water-soluble, solution-stable and biolabile prodrugs" ACTA PHARMACEUTICA NORDICA (1992), 4(1), 35-42, XP002249867 page 37, column 2, paragraph 2 page 41, column 2, paragraph 1 page 39; table 1	2,3
D5 Y	DE 10 37 451 B (SCHERING AG) 28 August 1958 (1958-08-28) column 1, paragraphs 1,2; examples 14,17 column 7, paragraph 1	1-5,8-26
D6 Y	WO 97/41144 A (SEARLE & CO ;TJOENG FOE S (US); CURRIE MARK G (US); ZUPEC MARK E () 6 November 1997 (1997-11-06) page 4, paragraph 1; examples 21,24	1-5,8-26
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D7 Y	WO 97 34871 A (GARVEY DAVID S ; LETTS L GORDON (US); NITROMED INC (US); RENFROE H) 25 September 1997 (1997-09-25) page 1, paragraph 1; examples 4,5 page 5, paragraph 1 page 3, paragraph 4	1-5,8-26
D8 Y	WO 98 15568 A (NICOX SA ; DEL SOLDATO PIERO (IT)) 16 April 1998 (1998-04-16) page 1, paragraphs 2,4; examples 1,3 page 2, paragraph 2	1-5,8-26
D9 P;X	WO 02 051385 A (NICOX SA ; DEL SOLDATO PIERO (IT); TRESPIDI LAURA (IT)) 4 July 2002 (2002-07-04) example 8	1,4,5, 9-26
D10 E	EP 1 336 602 A (SCARAMUZZINO GIOVANNI) 20 August 2003 (2003-08-20) page 90 and page 137, compound ECVIId page 167, pharmacological example 13 page 91 and page 137, compounds ECVIIb; page 91, compound ECVIIa; Pharmacological example 12 page 92, compound ECXCa; Pharmacological example 14 page 98 & page 129, compound JIIc; example 11 page 126, compound ECVIIa; examples 7,8 page 126, compound ECVIIIa; example 9 page 127, compound ECXCa; example 10 page 136, compound ELXVc ; pharmacological example 16, page 167 page 3, paragraphs 20,26,27 page 142, paragraph 73	1,4,5, 9-12,15, 17, 19-21, 23-26
D11 X	WO 00 61604 A (NICOX SA ; DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) examples 1,2 page 5, paragraph 1 page 36, paragraph 1 page 69; table II page 73; table VI page 7, line 16 -page 8, line 6 claim 1	1-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5,9-26 (in part) 8 (in full)

Corticosteroid nitrates without a carboxy group in position 17.beta, pharmaceutical compositions and uses thereof.

2. Claims: 1-4,9-26 (in part) 6 (in full)

Bile acid nitrate dervatives, pharmaceutical compositions and uses thereof.

3. Claims: 1-4,9-26 (in part) 7 (in full)

Estrogen nitrate dervatives, pharmaceutical compositions and uses thereof.

4. Claims: 1-5,9-26 (in part)

Glucocorticoid nitrate dervatives, with a carboxy group in position 17.beta, pharmaceutical compositions and uses thereof.

INTERNATIONAL SEARCH REPORT

international application No.
PCT/JP 03/00394

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 1037451	B	28-08-1958	CH 367496 A	28-02-1963
WO 9741144	A	06-11-1997	US 5837698 A	17-11-1998
			AT 197799 T	15-12-2000
			AU 2922797 A	19-11-1997
			CA 2253346 A1	06-11-1997
			DE 69703619 D1	04-01-2001
			DE 69703619 T2	03-05-2001
			DK 900233 T3	22-01-2001
			EP 0900233 A1	10-03-1999
			ES 2152670 T3	01-02-2001
			GR 3035088 T3	30-03-2001
			JP 2000509072 T	18-07-2000
			PT 900233 T	30-03-2001
			WO 9741144 A1	06-11-1997
WO 9734871	A	25-09-1997	US 5824669 A	20-10-1998
			AU 733202 B2	10-05-2001
			AU 2533697 A	10-10-1997
			CA 2248800 A1	25-09-1997
			EP 0904266 A1	31-03-1999
			JP 2000509016 T	18-07-2000
			WO 9734871 A1	25-09-1997
			US 6197762 B1	06-03-2001
			US RE37116 E1	27-03-2001
			US 2003199529 A1	23-10-2003
			US 6579863 B1	17-06-2003
WO 9815568	A	16-04-1998	IT MI962048 A1	06-04-1998
			AT 218142 T	15-06-2002
			AU 719250 B2	04-05-2000
			AU 4780397 A	05-05-1998
			BR 9711586 A	24-08-1999
			CN 1253563 A	17-05-2000
			DE 69712900 D1	04-07-2002
			DE 69712900 T2	12-12-2002
			DK 929565 T3	09-09-2002
			WO 9815568 A2	16-04-1998
			EP 0929565 A2	21-07-1999
			ES 2177952 T3	16-12-2002
			HU 9904149 A2	28-04-2000
			JP 2001501637 T	06-02-2001
			KR 2000048911 A	25-07-2000
			PT 929565 T	31-10-2002
			RU 2186781 C2	10-08-2002
			SI 929565 T1	31-08-2002
			US 6610676 B1	26-08-2003
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			WO 02051385 A1	04-07-2002
			EP 1347744 A1	01-10-2003
EP 1336602	A	20-08-2003	EP 1336602 A1	20-08-2003
WO 0061604	A	19-10-2000	IT MI990751 A1	13-10-2000
			AU 766798 B2	23-10-2003
			AU 3820100 A	14-11-2000
			BR 0009696 A	08-01-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0061604 A	CA	2370446 A1	19-10-2000
	CN	1420891 T	28-05-2003
	WO	0061604 A2	19-10-2000
	EP	1169337 A2	09-01-2002
	HU	0201872 A2	28-10-2002
	JP	2002542162 T	10-12-2002
	NO	20014925 A	13-12-2001
	PL	350775 A1	10-02-2003
	TR	200102929 T2	22-04-2002
	TR	200201899 T2	21-11-2002
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